REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 21-24, 26 and 27 will be active in the application subsequent to entry of this Amendment. The examiner has indicated claim 22 to be allowable while rejecting claims 25 (enablement) and 21, 23, 24 and 26 (lack of clarity). Only claim 27 is the subject of a prior art-based rejection.

In this Amendment, claim 21 is amended rendering claim 21 and the claims dependent from it clear, and claim 25 has been deleted in order to reduce issues. With the lack of clarity rejection, item 6 of the Official Action, resolved, it is counsel's understanding that claims 21-24 and 26 are in condition for allowance.

Amendments to the Specification and Claims

Page 2, line 2 of the specification has been amended to change "WO 97/21865" into "WO 97/28165".

Claim 25 has been deleted without prejudice or disclaimer in order to reduce issues.

Claim 21 is amended by deleting the term "or Y is $N+R_{12}R_{13}R_{14}$ as defined above".

Claim 25 – 35 U.S.C. § 112 first paragraph

The rejection has been obviated by the deletion of claim 25.

Claims 21 and 23-26 – 35 U.S.C. § 112 second paragraph

The rejection has been obviated by the amendment of claim 21.

Claim 27 – 35 U.S.C. § 103 – Penco in view of Matsumoto

Claim 27 is the only claim rejected on the basis of prior art. Applicant continues to rely on the previously presented arguments, which will not be repeated here, but explicit reference is made thereon.

The Examiner assumes that Matsumoto et al leaves no doubt regarding general applicability of this approach. This assumption shall be examined with the crucial factual inquiry set forth in *Graham vs. John Deere Co.* "Resolving the level of the skilled in the pertinent art".

In view of the above assumption, the Examiner concludes that the "one skilled in the art would have been motivated to prepare the prodrugs of camptothecin derivatives disclosed by Penco using spontaneously cleavable linker strategy disclosed by Matsumoto to enhance water solubility since Penco teaches problem of low water solubility of camptothecin derivatives for treating lung carcinoma". Applicant disagrees with this conclusion.

Before discussing the crucial factual inquiry of the level of the skilled person in the pertinent art, Applicant will discuss the scope and content of prior art.

a) Scope and content of the prior art.

As already discussed in the specification of the present invention, the problem of solubility of camptothecins was already faced and solved in the prior art. Specification, page 1, last paragraph, cites US 4,943,579 (briefly, US '579) which discloses water soluble camptothecins. This document is attached for the Examiner's convenience. The person skilled in the art of camptothecins will learn from this reference that previous attempts to modify the camptothecin molecule in order to provide water solubility were unsuccessful (see col.1, line 34, to col. 3, line 19) and subsequent modifications of the molecule did not disclose enhancement of water solubility. The reference provides a solution to the problem of water solubility of camptothecins by transforming the hydroxy group in position 20 of the lactone ring E. This reference demonstrates to have solved the technical problem in a satisfactory way; *see* Tables 1 and 2.

Therefore, the skilled person would find substantial motivation to modify camptothecins disclosed by Penco et al. according to the teaching of US '579.

As a further teaching of the prior art, the skilled person will find Singer J.W., et al., Anticancer Drug Design (1999), 14, 499-506 (see page 2 of the specification), wherein hydrosoluble conjugates of camptothecins with polyglutamica acid-glycine are disclosed. This reference also provides a good motivation to modify Penco et al.'s compounds accordingly.

No other references on water soluble camptothecins have been discovered in the specification, or in the International Search Report, or by the present Examiner.

Accordingly, the scope and content of the state of the art is as defined above. The prior art provides the skilled person good solutions to the technical problem of preparing water soluble camptothecins. Therefore, the skilled person has no motivations to find alternatives which are not available in the art. Doing so, this person will qualify as inventor, deserving patent protection.

b) The difference between the prior art and the claims at issue.

As already discussed in the previous papers, the difference between the art (Penco et al.) and the claims at issue is the group $-CO-A-(CO)_n-(NH)_m-Y$. This group is never mentioned in the art of camptothecins.

c) The level of the skilled person.

Examiner will agree on the fact that medicinal chemistry is an art affected by a high level of unpredictability and that a large amount of experimentation is necessary to find, prepare and test new drugs. On this assumption, Applicant recognized the Examiner's reasons in the objection under section 112, first paragraph and deleted claim 25.

The skilled person, confronted with the problem of providing water soluble camptothecins which are still endowed with antitumor activity will find a good solution to the problem in the above mentioned US 4,943,579.

Thus, the skilled person will rely on US '579, which gives full information on how to prepare camptothecin derivatives (col. 5 and 6) starting from Penco et al. The skilled person will note that the process for the preparation of water soluble derivatives disclosed in US '579 does not affect the 7-substituent, characteristic of Penco et al.'s compounds.

The problem of hydrosoluble camptothecin derivatives is not explicitly faced in Penco et al. Apparently, the problem is not solved with means different than the ones provided in the state of the art, namely inserting in the molecule hydrophilic groups. For example hydroxy, NH_2, -COOH in R_1; hydroxy or NH_2, polyaminoalkyl, glycosyl in R_4; hydroxyl for R_2 and R_3.

The level of the skilled person is of the one who, as soon as a good solution to the technical problem is found, will not continue searching in the art, unless a specific motivation is stated in the art just found.

The art of water soluble camptothecins is self-contained. There is no motivation in this art to search in other fields (namely different families of drugs with a totally different molecular structure).

Examiner will note that also Matsumoto et al. include a discussion on solubilizing HIV protease inhibitors in a self-contained manner, namely studying the prior art concerning solubilization of these specific drugs (Matsumoto et al., page 605, first and second columns).

Applicant cannot agree with the Examiner on the relevance of Matsumoto. The person skilled in the art is aware that in medicinal chemistry the knowledge concerning a certain family

of drugs, taken from the chemical structural point, cannot be transferred "as such" to another family. A verification process must be taken with ample range of experimentation in order to verify the possibility of such a transfer.

In case of the present invention, the Examiner searched in the prior art the relevant documentation. The following documents resulted from the search: US 4,943,579 (cited in the description), Penco et al.'s patent and Matsumoto.

It is Applicant's belief that the Examiner considered Matsumoto et al. with the foreknowledge of the claimed invention. In fact, the reference is linked to the claimed invention only (and only) for the moiety represented in formula (I), $-CO-A-(CO)_n-(NH)_m-Y$.

Since the skilled person is not aware of the claimed invention before undertaking his/her research, applicant wonders whether how this person would have arrived at the claimed invention and, especially, would have retrieved Matsumoto and for which reason.

The skilled person will undertake studying the technical problem with the background of a general common knowledge concerning his field of activity. In this case, the field is medicinal chemistry. To illustrate this point, attached is an excerpt from an Italian University Handbook of Medicinal Chemistry dealing with the influence of functional groups on drug activities. The examiner will note the part relevant to carboxylic acids and basic groups (amino), which are part of the present invention.

In the part relating to the carboxylic groups (page 170, section 5, underlined part), the handbook says "The introduction of carboxylic groups in a base molecule essentially has two consequences: the possibility of making the molecule water-soluble (whenever this molecule is insoluble or poorly soluble in water) through the salification of the carboxy group; general lowering of existing pharmacological activity." (emphasis added).

In the part relating to the basic groups (page 171, section 7, underlined part), the handbook states "The introduction of basic centers in a molecule backbone generally implies consequences: the possibility of making the molecule water-soluble (whenever this molecule is insoluble or poorly soluble in water) through the salification of the carboxy group; important and not always foreseeable modifications of biological activity." (emphasis added).

In the part relating to the various groups (page 174, section 9, underlined parts), the handbook instructs "Generally, one can argue from the above discussion that a forecast of a

modification of biological activity of a certain base molecule following the introduction of new functional groups is not only not easily possible, but often quite impossible or provides only generic indications. (emphasis added). [...] For usual functional groups, forecasts are even more difficult because of the completely different biological activity." (emphasis added).

With this knowledge in his mind, the skilled person will be guided in his search for a solution to the technical problem of making available a camptothecin derivative such as those of Penco et al., but without affecting pharmacological activity.

Therefore, the skilled person will look into the prior art concerning camptothecin derivatives.

As far as this aspect is concerned, the skilled person will take into consideration the above mentioned US '579. This document, already discussed by the Examiner, provides a different solution to the problem of hydrosoluble camptothecin derivatives. And, the skilled person will find good data on antitumor activity of the modified compounds.

Having in mind that a modification of a base molecule with functional groups could have unpredictable effects on its pharmacological activity, and that the general knowledge warns about possible lowering of such activity by introducing further chemical groups, the person of ordinary skill in the art would be very cautious in paying attention to the problem of water-soluble camptothecin derivatives with a possibly lower antitumor activity. In this particular case, the skilled person is conscious that the compounds disclosed in Penco et al. have a high value in the field of camptothecins because of their higher antitumor activity. A representative member of this class of compounds is represented by Gimatecan (see the enclose paper by Pratesi et al.).

In fact, the technical problem of the skilled person is to provide a water-soluble derivative of Penco et al., but without affecting antitumor activity. This task is demanding, since Penco et al. provides a solution for preparing aqueous formulations for administration (Col. 12, lines 28-31).

Accordingly, the skilled person, in the absence of the any confirmation that modified water soluble derivatives of camptothecins maintain the same or similar antitumor activity, would have refrained to try any other modification, knowing that modification of lactone ring of camptothecins is at risk of loosing or lowering antitumor activity.

Other possible information comes from US '579, in which the 20-hydroxy group is esterified either with a dicarboxylic acid or an amino acid. The results could also be satisfactory, see Tables 1 and 2. See in particular compound 14. Taking into account this teaching, the skilled person would have modified Penco et al.'s compounds accordingly, namely by esterifying the 20-hydroxy with a bicarboxylic acid. In this way, the skilled person would not have arrived yet at the present invention.

Without the foreknowledge of the present invention, the skilled person would not have searched in a field different from that of the camptothecins, thus would not have retrieved Matsumoto.

There is no reason that the skilled person takes any risk in further modifying such a critical portion of camptothecin molecule, i.e. the lactone ring. Once this person achieves the result, no further activity is requested of him. Then, combining Penco and US '579, the technical result is not the claimed invention, but something different.

In the unlikely event the skilled person, with no knowledge of the claimed invention would have retrieved Matsumoto reference, he would have understood that it relates only to HIV RP inhibitors of dipeptide nature. This reference says nothing on the applicability of its teaching to other drugs. Of more importance, this reference says nothing on the pharmacological activity of the modified drug, this being a critical aspect of the technical problem of the present invention.

The generic statements identified by the Examiner in Matsumoto cannot be taken as a rigorous teaching, as the skilled person needs, to be applied to camptothecins. The skilled person knows that any intervention on the lactone ring bears the serious risk to compromise the antitumor activity of the drug, therefore, without a clear indication to do so in Matsumoto, this person would avoid following this teaching, especially in view of the positive teaching provided by US '579.

Of concern, Matsumoto explains the mechanism of intramolecular cyclization-elimination in order to release the drug. There is no guarantee in Matsumoto that this mechanism would not affect lactone ring of camptothecin, possibly destroying the antitumor activity.

Therefore, the skilled person, albeit not motivated to search Matsumoto, would not have followed this teaching, since between a positive teaching of the art (Penco and US '579) and an undetermined teaching of Matsumoto, this person would have chosen the positive one.

The level of skill of this person is to find a solution in the art and to follow it. No other trials and experimentation are requested to this person.

For the above reasons it is respectfully submitted that claims 21, 23, 24, 26 and 27 are allowable. If for any reason this is not the case, the examiner is encouraged to contact the undersigned by telephone.

Submitted with this response is a PTO/SB/08a listing the two documents discussed in the above remarks so that the record of this application will be clear that the documents have been taken into account during the review and continuing examination of this application.

Respectfully submitted,

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